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SYSTEMATIC REVIEW AND META-ANALYSIS

Maternal and Neonatal Outcomes of Pregnancies in Women With Congenital Heart Disease: A Meta-Analysis

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BACKGROUND: With advances in the treatment of congenital heart disease (CHD), more women with CHD survive childhood to reach reproductive age. The objective of this study was to evaluate the maternal and neonatal outcomes of pregnancies among women with CHD in the modern era.

METHODS AND RESULTS: We conducted a meta-analysis of peer-reviewed literature published January 2007 through June 2019. Studies were included if they reported on maternal or fetal mortality and provided data by CHD lesion. Meta-analysis was performed using random effect regression modeling using Comprehensive Meta-Analysis (v3). CHD lesions were categorized as mild, moderate, and severe to allow for pooling of data across studies. Of 2200 articles returned by our search, 32 met inclusion criteria for this study. Overall, the rate of neonatal mortality was 1%, 3.1%, and 3.5% in mild, moderate, and severe lesions, respectively. There were too few maternal deaths in any group to pool data. The rates of maternal and neonatal morbidity among women with CHD increase with severity of lesion. Specifically, rates of maternal arrhythmia and heart failure, cesarean section, preterm birth, and small for gestational age neonate are all markedly increased as severity of maternal CHD increases.

CONCLUSIONS: In the modern era, pregnancy in women with CHD typically has a successful outcome in both mother and child. However, as maternal CHD severity increases, so too does the risk of numerous morbidities and neonatal mortality. These findings may help in counseling women with CHD who plan to become pregnant, especially women with severe lesions.

Key Words: cardiac arrhythmia ■ congenital heart disease ■ congestive heart failure ■ meta-analysis ■ pregnancy

Congenital heart disease (CHD) is the most common congenital disorder, occurring in 81 in every 10 000 births.[1] Advances in the identification and treatment of CHD have improved the long-term survival of patients. Consequently, more women with CHD survive childhood to reach reproductive age. Most women with CHD will conceive and tolerate pregnancy well, but for those with complex CHD, pregnancy presents a higher-than-average risk to both the mother and her fetus.[2]

The physiologic hemodynamic changes of pregnancy include increased blood volume and cardiac output, reduced peripheral vascular resistance, and hypercoagulability. In the context of both uncorrected congenital heart defects and corrected cardiac lesions, the specific risk of arrhythmia, stroke, and maternal death appears to be increased.[3] Prior systematic reviews have identified a dose-dependent relationship between severity of cardiac disease and maternal cardiac complications including heart failure, hypertensive syndromes, premature delivery rate, and delivery of a small for gestational age (SGA) infant.[4]

The last systematic review of pregnancy outcomes in women with CHD was published in 2007.[4] An updated meta-analysis would better inform physicians and patients with CHD who hope to become pregnant

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CLINICAL PERSPECTIVE

What Is New?

- Through an analysis of 32 articles, we found greater mortality among neonates born to women with more severe congenital heart disease, as well as higher rates of morbidity among neonates born to mothers with congenital heart disease.
- These data are important because no statistical evaluation of these risks has been performed in the modern era.

What Are the Clinical Implications?

- These findings may guide counseling and practice in the treatment of pregnant women with congenital heart disease.

Nonstandard Abbreviations and Acronyms

TGA	transposition of the great arteries
ToF	tetralogy of Fallot

or who desire contraceptive or abortive care and would help to identify opportunities for improvement in treatment. The objective of this study is to evaluate the maternal and neonatal outcomes of pregnancies among women with CHD in the modern era. We hypothesize that women with more severe CHD will have greater risk of adverse pregnancy outcomes relative to those with more mild CHD.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

We searched peer-reviewed literature published between January 2007 and June 2019 to identify published English-language articles pertaining to the outcomes of pregnancies of mothers with CHD. We conducted a review of Ovid MEDLINE, EMBASE, and Cochrane Library databases according to the Preferred Reporting for Systematic Reviews and Meta-Analyses guidelines.[5]

A search strategy was implemented using terms pertaining to CHD, pregnancy, and maternal and neonatal outcomes in order to answer the study question: Do women with more severe CHD have worse outcomes? These terms included the following: pregnancy, labor, delivery, pregnancy complication, maternal death, maternal mortality, congenital heart defects, septal defects, valve stenosis, fetal mortality, premature birth, and SGA (Table S1). Predefined limits required that a study's complications be delineated by CHD type and that the number of completed pregnancies (not aborted or miscarried) for the primary CHD category must be available. In contrast, studies aggregating all types of CHD when reporting complications were excluded. The primary outcomes required for inclusion were defined as maternal (variably defined by respective authors, ranging from within pregnancy to within the first year after delivery) or fetal mortality (defined as infant demise within the first 28 days of life), with data delimited by CHD lesion type. Randomized controlled trials, cohort studies, cross-sectional studies, and case series were considered for review. Case reports and studies describing ≤1 completed pregnancy were deemed ineligible because of their limited sample size. Additional reports were identified through cross-reading relevant reference lists. The available reports were screened independently by 2 researchers (I.H. and L.W.) as described in Figure. When discrepancies between the 2 researchers were discovered, a third independent cardiologist (M.O.) served as a tie-breaker. Publications from the same institution were checked for period of data collection and duplicates, and those with overlapping data were excluded. A total of 45 studies were analyzed for overlapping data, which led to the elimination of 11 because of population coverage by another publication, yielding a total of 34 papers ultimately analyzed.

Statistical Analysis

Covidence Meta-Analysis program was used for organizing meta-analysis screening. Meta-analysis was performed via random effect regression modeling using Comprehensive Meta-Analysis (v3). CHD lesions were analyzed as independent entities when ≥4 estimates of the risk of a dependent outcome were available.[6] Lesions were included in the analysis if there were 5 or more total citations reporting on that lesion and those citations met inclusion criteria (Tables S2 and S3). Further, in accordance with a recent study on long-term outcomes of patients with CHD, lesions were categorized as mild, moderate, and severe to allow for pooling of data across studies.[7] Mild lesions included atrial septal defect, patent ductus arteriosus, and ventricular septal defect; moderate lesions included coarctation of the aorta, Ebstein's anomaly, pulmonic stenosis, and tetralogy of Fallot (ToF); severe lesions included double-outlet right ventricle, history of a Fontan palliation procedure (Fontan), pulmonic atresia, transposition of the great arteries (TGA), and Eisenmenger's syndrome.

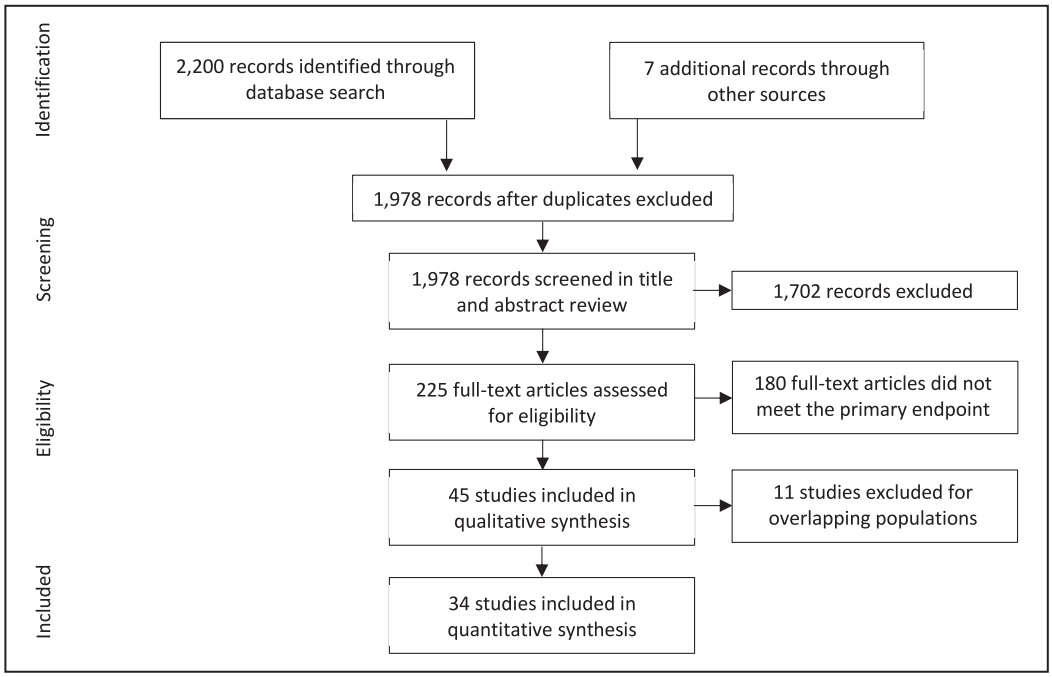

Figure. Flow chart of study selection.

When there were too few events for pooling estimates (ie, too many studies reported 0 events), data were summarized by tabulating the total number of patients, the total number of events, and the event rate (number of events/number of patients)×100%, and exact 95% binomial CIs were computed. For studies reporting 0 events, the event rate was imputed to 0.001 to allow for estimation of the variance. Although this imputation inflated the variance estimate, studies with imputed event rates were pooled only when there were a sufficient number of other studies with nonzero event rates (>50% of studies); otherwise, the data were summarized using the method described. When there were a sufficient number of events to allow for pooling estimates, event rates were summarized as percentages with associated 95% CIs obtained from random-effects regression. Measures of heterogeneity including the I^2 statistic and Cochran's Q were computed to determine the degree of heterogeneity between studies both within and across CHD severity groupings.

To assess the robustness of the results, 2 types of sensitivity analyses were performed. First, to examine the impact of an alternative classification scheme on the results, the original pooled estimates for maternal and neonatal outcomes were reanalyzed using the classification scheme for simple, moderate, and complex lesions from Stout et al.[8] Second, to examine the influence of any one study on the overall pooled estimate from regression, studies were systematically removed one at a time, and the overall effect size was recomputed with the single study excluded. Effect sizes with 1 study removed were then compared with the original estimate and its CI. When the removal of a single study resulted in a recomputed effect size outside the original 95% confidence limits, potential bias resulting from a single study was noted. Publication bias was assessed using the Begg and Madzumdar rank correlation coefficient and via visual inspection of the forest plots when >10 studies were available for pooling. Begg and Madzumdar rank correlation test provides a nonparametric measure of association, Kendall's Tau, between the study effect size and theSE. Statistical significance was assessed at the 0.05 level, unless otherwise noted. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Literature Search and Study Characteristics

A total of 34 studies including 23 retrospective cohort studies, 3 prospective cohort studies, and 8 case series were pooled for this meta-analysis. There were 2770 women with CHD and 3491 pregnancies included in the study. Thirty-two of the studies reported on maternal outcomes and 29 of the studies reported data on neonatal outcomes. Among these studies 25 were conducted outside the United States and 8 within, whereas 1 reported data both domestically and internationally (Table 1).[9–42] Women described were treated in centers ranging from rural hospitals to tertiary care centers.

Patient Characteristics

The most common CHD diagnoses studied were ToF, atrial septal defect, and coarctation of the aorta. The average age of the populations meta-analyzed was between 21 and 30 years of age.

Maternal Outcomes

Maternal Mortality

A total of 27 studies reported data on maternal mortality across 1347 pregnant women with CHD. These 1347 women spanned 14 different CHD lesions (aortic stenosis, atrial septal defect, congenitally corrected TGA, coarctation of the aorta, double-outlet right ventricle, Ebstein's anomaly, Eisenmenger's syndrome, Fontan, pulmonary atresia, patent ductus arteriosus, pulmonic stenosis, TGA, ToF, and ventricular septal defect). Across all 27 studies, there were only 9 total reported events of maternal mortality. In studies that reported cause of maternal death the most common cause was "uncontrollable heart failure" followed by sudden cardiac arrest. Because of the small number of events in this category, data were not pooled using random-effects modeling but instead presented as total number of events divided by the total number of patients with exact 95% CIs (Table 2). Of maternal mortality cases, the majority (8/9) occurred in women with severe lesions. Studies reporting maternal mortality reported that women with Eisenmenger's syndrome and TGA in their populations had the highest rates of mortality at 13.0% and 1.1%, respectively (Table S4).

Arrhythmia

A total of 23 studies reported data on arrhythmia across 1954 pregnant women with CHD. There were a total of 109 reported events of arrhythmia. Results from the random effect regression showed substantial heterogeneity in the pooled rates of arrhythmia across CHD severity groups (P=0.001). Women with severe CHD had the highest rates of arrhythmia followed by moderate and mild lesions (Table 2). When examining individual lesions, arrhythmia was most common in Eisenmenger's syndrome (39.4%) followed by Ebstein's anomaly (20.9%), TGA (11.8%), and Fontan (10.3%) (Table S4).

Heart Failure

A total of 21 studies reported data on heart failure across 1904 pregnant women with CHD. A total of 70 heart failure events were reported. Significantly higher rates of heart failure were diagnosed in the severe (15.2%) relative to the moderate (2.8%) group (P<0.001) (Table 2). When examining individual lesions, heart failure was most commonly reported among pregnant women with Eisenmenger's (69.5%), followed by Fontan (6.1%), Ebstein's anomaly (5.6%), TGA (6.1%), and ToF (2.8%) (Table S4).

Hypertensive Diseases of Pregnancy

A total of 16 studies reported data on hypertensive diseases of pregnancy, including gestational hypertension, preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelet count syndrome. These studies found 187 events among 1729 pregnant women with CHD. Rates of developing hypertensive diseases of pregnancy were not significantly different among the mild, moderate, and severe groups (Table 2). Women with a history of Fontan were analyzed individually, developing hypertensive diseases of pregnancy at a rate of 3.6% (Table S4).

Postpartum Hemorrhage

A total of 15 studies reported data on postpartum hemorrhage across 1737 pregnant women with CHD. A total of 172 cases of postpartum hemorrhage were diagnosed, without significant differences in event rate across the mild, moderate, and severe CHD groups (Table 1). Begg and Madzumdar rank correlation show significant publication bias among the severe group. Postpartum hemorrhage rates were individually analyzed in women with Fontan and ToF, revealing rates of 11.2% and 8.7%, respectively (Table S4).

Thromboembolic Events

A total of 19 studies reported data on thromboembolic events across 1102 pregnant women with CHD. Among this population there were 13 reported cases. There were qualitatively more events in the severe CHD group (Table 2). When examining individual lesions, women with Eisenmenger's most frequently experienced thromboembolic events (3.6%), followed by those with TGA (1.0%) and ToF (0.5%) (Table S4).

Cardiac Arrest

A total of 8 studies reported data on cardiac arrest across a population of 353 women. Of those, none had reported cardiac arrest (Table 2).

Endocarditis

A total of 10 studies reported data on endocarditis across a population of 1496 pregnant women with

Table 1. Characteristics of Populations Included in the Meta-Analysis

Study name	Atrial Stenosis	Atrial Septal Defect	Congenitally Corrected TGA	Coarctation of the Aorta	Double-Outlet Right Ventricle	Ebstein's	Eisenmenger's	Fontan	Pulmonary Atresia	Patent Ductus Arteriosus	Pulmonary Stenosis	TGA	Tetrology of Fallot	Ventricular Septal Defect	Total Pregnancies	Mean Age at Delivery	First Year of Inclusion	Population Origin
Balci et al (2014)[9]	29	21	1	26		4		3			22	15	40	26	213	28.7	2008	Non-US
Bonner et al (2017)[10]								9							19	23	2004	Non-US
Brun (2020)[11]											12		33		97	28.8	1997	Non-US
Cataldo et al (2016)[12]												21			34	26	1993	Non-US
Cauldwell et al (2018)[13]								50							124	27	2005	Non-US
Chopra et al (2010)[14]						4									8	26.3	1993	Non-US
Drenthem et al (2008)[15]					10										19	30	1980	Non-US
Drenthen et al (2010)[16]	81	188	19	160		22	4	9	12			52	124	148	1302	27.4	1980	Non-US
Duan et al (2016)[17]							11								11	25.7	2010	Non-US
Egbe et al (2019)[18]									13		31		70		224	26	1990	US
Ford et al (2008)[19]	5	10		7	1	2		1		2	3	5	13	5	74	28	2000	US
Gelson et al (2008)[20]													16		26	26.4	1996	Non-US
Gelson et al (2011)[21]												14			19	29.1	1996	Non-US
Gouton et al (2015)[22]								37							59	27	2000	Non-US
Hidano et al (2011)[23]	Maternal lesions of 128 total women unspecified (lesions specified only in relation to pregnancies)														151	Unknown	1998	Non-US
Jain et al (2011)[24]	Maternal lesions of 114 total women unspecified (lesions specified only in relation to pregnancies)														146	27.9	1998	US
Jimenez-Juan et al (2014)[25]				28											30	29	1996	Mixed
Kampman et al (2017)[26]													62		62	31	2008	Non-US
Katsuragi et al (2013)[27]						13									27	31.3	1985	Non-US
Katsurahgi et al (2019)[28]							15								15	29.9	1982	Non-US

(*Continued*)

Table 1. Continued

Study name	Atrial Stenosis	Atrial Septal Defect	Congenitally Corrected TGA	Coarctation of the Aorta	Double-Outlet Right Ventricle	Ebstein's	Eisenmenger's	Fontan	Pulmonary Atresia	Patent Ductus Arteriosus	Pulmonary Stenosis	TGA	Tetrology of Fallot	Ventricular Septal Defect	Total Pregnancies	Mean Age at Delivery	First Year of Inclusion	Population Origin
Kowalik et al (2014)[29]			13												20	27.3	1991	Non-US
Ladouceur et al (2017)[30]							17		3						28	26	1997	Non-US
Metz et al (2011)[31]												10			21		1999	US
Michaelson-Cohen et al (2011)[32]	4	13				1		2					3	15	38	29.4	1994	Non-US
Pedersen et al (2008)[33]													25		54	Unknown	1972	Non-US
Phillips et al (2019)[34]								7							13	27.5	2002	US
Pillutla et al (2016)[35]	Maternal lesions of 43 total women unspecified (lesions specified only in relation to pregnancies)														61	27	1994	US
Pundi et al (2016)[36]								19							29	27.7	1973	US
Song et al (2008)[37]		15				3			1	1	2		3	9	49	29.8	1995	non-US
Tobler et al (2010)[38]												9			17	21	2000	Mixed
Wang et al (2011)[39]							13								13	27.2	2001	Non-US
Yap et al (2009)[40]		100													243	28.4	1980	Non-US
Yap et al (2010)[41]														88	202	28.2	1980	Non-US
Zentner et al (2012)[42]												19			43	Unknown	Unknown	Non-US
Total	119	347	33	221	11	49	60	137	29	3	70	145	389	291	3491			

TGA indicates transposition of the great arteries; and US, United States.

CHD. Of those, 4 women had reported cases of endocarditis (Table 2).

Neonatal Outcomes

Neonatal Mortality

A total of 27 studies reported data on neonatal mortality across 2044 pregnancies. There were a total of 44 deaths reported. Because of the number of studies reporting zero events, results were not pooled for comparison (Table 3). When examining individual lesions, there were too few events to pool estimates (except in the case of atrial septal defect). Raw rates with associated exact 95% CIs are presented in Table S4. The highest rates of neonatal mortality were observed in women with Ebstein's anomaly, Eisenmenger's syndrome, Fontan, TGA, and CoA.

Cesarean Section

A total of 20 studies reported data on the rate of cesarean section (C-section) across 860 pregnancies. There were a total of 245 C-sections reported. Random-effects regression analysis demonstrated that women with severe CHD (52.5%) and moderate CHD (30.8%) had higher rates of C-section delivery relative to those with mild CHD (22.5%) (P=0.025) (Table 3). Among the pooled cohort, the highest rates of C-section were observed among women with a history of Fontan and Eisenmenger's syndrome (Table S5).

Miscarriage/Spontaneous Abortion

A total of 17 studies reported data on the rates of miscarriage or spontaneous abortion among 1285 pregnancies to women with CHD. There were too few studies to pool data among women with mild CHD, however there was a significantly higher rate of miscarriage or spontaneous abortion among women with severe CHD (33.7%) relative to those with moderate CHD (16.1%) (P=0.004) (Table 3). Among the pooled cohort, women with a history of Fontan had the highest rate of pregnancy loss (Table S5).

Preterm Delivery

A total of 23 studies reported data on the rate of preterm or premature delivery (delivery before 37 weeks estimated gestation) among 1759 pregnancies. There were a total of 306 preterm births. Random-effects regression analysis demonstrated that pregnancies of women with severe CHD (50.5%) and moderate CHD (13.9%) were significantly more likely to be premature than those of women with mild CHD (5.8%) (P<0.001) (Table 3). Preterm births were most common among women with Eisenmenger's syndrome and Fontan (Table S5).

Recurrence

A total of 23 studies reported data on the rate of recurrence of a CHD diagnosis in 1075 offspring of women with CHD. Of these offspring, 33 were affected by recurrence of CHD. Pooled estimates reveal a nonsignificant

Table 2. Summary of Pooled Estimates of Maternal Outcomes by CHD Lesion Severity

Estimated 95% CI N Studies/ Lesions	Maternal Outcome							
Severity Group	Maternal Mortality	Arrhythmia	Cardiac Arrest	Endocarditis	Heart Failure	Hypertensive Disease of Pregnancy	Postpartum Hemorrhage	Thrombolytic Event
Mild*	1/243† 0.4 (0.01–2.3)‡ N=15	3.2 (2.0–5.0) N=7	0/69† 0.0 (0.00–5.21)‡ N=6	2/700† 0.3 (0.0–1.03)‡ N=6	6/705† 0.9 (0.3–1.84)‡ N=7	11.3 (9.2–14.0) N=4	10.4 (8.3–13.0) N=6	4/372† 1.1 (0.3–2.7)‡ N=4
Moderate§	0/540† 0.0 (0.0–0.7)‡ N=26	8.1 (4.1–15.3) N=12	0/134† 0.0 (0.00–2.72)‡ N=9	1/520† 0.2 (0.00–1.07)‡ N=7	2.8 (1.1–7.3) N=12	11.8 (8.9–15.5) N=7	10.6 (8.3–13.5) N=8	3/295† 1.0 (0.2–2.9)‡ N=7
Severe‖	8/462† 1.7 (0.8–3.4)‡ N=27	12.6 (7.4–20.7) N=17	0/79† 0.0 (0.00–4.56)‡ N=9	1/172† 0.6 (0.00–3.20) N=10	15.2 (7.4–28.8) N=15	10.3 (5.2–19.4) N=12	39/357† 10.9 (7.9–14.6)‡ N=12	6/370† 1.6 (0.6–3.5)‡ N=14
P value	…	0.001	…	…	0.018	0.176	0.921	…

Blank cells indicate inadequate data to pool estimates. CHD indicates congenital heart disease.

*Mild: atrial septal defect, patent ductus arteriosus, and ventricular septal defect.

†For studies with too few events or >50% of studies reported zero events, the number of events and total sample size are reported along with unweighted event rate (%).

‡95% CIs are presented as exact CIs.

§Moderate: coarctation of the aorta, Ebstein's, pulmonary stenosis, tetralogy of Fallot.

‖Severe: double-outlet right ventricle, Fontan, pulmonary atresia, transposition of the great arteries, Eisenmenger's.

Table 3. Summary of Pooled Estimates of Neonatal Outcomes by CHD Lesion Severity

Estimated 95% CI N Studies/ Lesions	Neonatal Outcome						
Severity Group	Neonatal Mortality	Cesarean Section	Miscarriage/ Spontaneous Abortion	Preterm Delivery	Recurrence	Small for Gestational Age	Therapeutic Abortion
Mild*	8/773† 1.0 (0.5–2.0)‡ N=12	22.5 (12.3–37.7) N=5	§	5.8 (4.3–7.9) N=4	8/364† 2.2 (1.0–4.3)‡ N=4	14.6 (11.0–19.2) N=4	§
Moderate‖	22/700† 3.1 (2.0–4.7) N=17	30.8 (19.3–45.3) N=9	16.1 (10.6–23.6) N=7	13.9 (11.4–17.0) N=9	16/390† 4.1 (2.4–6.6)‡ N=9	13.8 (9.3–20.1) N=9	§
Severe¶	14/395† 3.5 (2.0– 5.9)‡ N=25	52.0 (35.8–67.8) N=12	33.7 (24.2–44.7) N=10	50.5 (36.4–64.6) N=17	9/297† 4.7 (2.6–7.9)‡ N=15	35.8 (24.0–49.6) N=14	9.5 (2.2–32.9) N=6
P value	…	0.025	0.004	<0.001	…	0.001	…

Blank cells indicate inadequate data to pool estimates.
*Mild:atrial septal defect, patent ductus arteriosus, and ventricular septal defect.
†For studies with too few events or >50% of studies reported zero events, the number of events and total sample size are reported along with unweighted event rate (%).
‡95% CIs are presented as exact CIs.
§Not enough studies to pool estimates (<3 studies).
‖Moderate: coarctation of the aorta, Ebstein's, pulmonary stenosis, tetralogy of Fallot.
¶Severe: double-outlet right ventricle, Fontan, pulmonary atresia, transposition of the great arteries, Eisenmenger's.

rate of CHD recurrence among offspring of women with severe CHD relative to those with moderate or mild disease (Table 3). Recurrence was most common among offspring of women with ToF and Fontan (Table S5).

Small for Gestational Age

A total of 20 studies reported data on the rate of a pregnancy to a woman with CHD being SGA among 1689 total pregnancies. A total of 292 pregnancies were SGA. Pooled estimates reveal a significantly higher rate of SGA infants born to women with severe CHD (35.8%) relative to those with mild (14.6%) and moderate (13.8%) CHD (*P*=0.001) (Table 3). Among lesions pooled for analysis, SGA pregnancies were most often identified among the Eisenmenger's syndrome and Fontan populations (Table S5).

Therapeutic Abortion

A total of 12 studies reported data on the rate of therapeutic abortion among 920 women with CHD. A total of 45 therapeutic abortions were reported with a significant degree of heterogeneity among pooled studies (I^2=86.25) (Table 4).

Study Heterogeneity

Results from the analysis of study heterogeneity are presented in Tables 4 and 5 for maternal and neonatal outcomes, respectively, and are presented only for outcomes where data could be pooled using random-effects models. For several of the maternal outcomes including arrhythmia, heart failure, and hypertensive disease of pregnancy, there was a moderate to substantial degree of heterogeneity among the study estimates as indicated by an I^2 value >30% and >50%, respectively. In addition, Cochran's Q value was also significant for many of these outcomes and lesion severity groupings. This further justified the use of random-effects modeling to pool study estimates when possible. In contrast, postpartum hemorrhage was an outcome with little to no heterogeneity. Neonatal outcomes with significant heterogeneity in outcome estimates included C-section, miscarriage/spontaneous abortion, preterm delivery, SGA, and therapeutic abortion.

Sensitivity Analysis

In the first sensitivity analysis examining the alternative classification scheme for simple, moderate, and complex lesions, there were minor differences in point estimates but no significant differences in overall findings or conclusions (data not shown). The results of the sensitivity analysis to examine the influence of any one study on the overall pooled estimate from regression are presented in Tables 4 and 5 for maternal and neonatal outcomes, respectively. The tables provide the minimum pooled effect size and the maximum pooled

effect size after removing any single study. These range of values were then compared with the original estimate and its 95% CI. For all maternal and neonatal outcomes, the range of recomputed effect sizes all fell within the CI of the original estimate.

Publication Bias

Publication bias was examined using the Begg and Madzumdar rank correlation coefficient (Tables 4 and 5). In addition, for cases in which estimates were pooled using 10 or more studies, funnel plots were included (Figures S1A through S1E and S2A through S2D).

Regarding maternal outcomes, Begg and Madzumdar's correlation demonstrated a significant ($P<0.05$) or near significant ($P<0.1$) association between the outcome rate and the SE of heart failure in the moderate and severe CHD severity groups. Further inspection of the funnel plots (Figure S1A through S1E) for outcomes with 10 or more studies and adequate event rates for pooling estimates revealed no major evidence of publication bias with the exception of patients with severe CHD and heart failure. In 2 studies of patients with Eisenmenger's syndrome, all pregnant women (100%) were reported to have heart failure, thus leading to an imbalance in the forest plot. In addition, the possible publication bias for heart failure in moderate CHD was likely driven by the number of studies reporting 0 events, which artificially inflated the SE (Figure S1C) regardless of the size of the study.

Regarding neonatal outcomes, Begg and Madzumdar's correlation demonstrated a significant ($P<0.05$) or near significant ($P<0.1$) association between the outcome rate and the SE for the following outcomes and subgroups: miscarriage/spontaneous abortion in severe CHD and preterm delivery in moderate CHD. Further examination of the funnel plots showed no clear evidence of publication bias for the outcome neonatal mortality for any of the lesion groups. The correlation between SE and event rate was driven by the large number of studies reporting 0 events, which results in inherently higher SEs owing to the low event rate. For the outcome of miscarriage (Figure S2B), there was a trend noted in the funnel plot as studies with larger SEs had lower event rates. No other funnel plots revealed evidence suggesting publication bias.

Study Quality

Level of evidence was assessed using the Methodological Index for Non-Randomized Studies rating scale (Table S6).[43] For noncomparative cohort studies, the maximum possible score was 16 points. The median (25th–75th percentile) score was 12 (11–14). Two studies (Balci, 2014; Ladouceur, 2017) scored 16 points.[9,30] The most commonly missed items were "unbiased assessment of the study end point" and "prospective calculation of the study size." For comparative studies the maximum possible score was 24 points. The median score was 20.5 (18–22). Only 1 study (Kampman, 2017) scored 24 points.[26] Most common missed items were "prospective calculation of the study size" and "adequate statistical analyses."

DISCUSSION

This meta-analysis evaluates the association between CHD severity and report of adverse pregnancy outcomes and is the largest review of its kind to be published. In the modern era, pregnant women with CHD can successfully carry a pregnancy to delivery with low rates of mortality. However, there

Table 4. Summary of Heterogeneity, Sensitivity Analysis, and Publication Bias for Pooled Neonatal Outcomes

Outcome	Group	Number of Studies	I^2	Cochran's Q (*P* Value)	Sensitivity Analysis (Min–Max)	Begg and Madzumdar Rank Correlation—Tau (*P* Value)
Cesarean section	Mild	5	84.50	25.80 (<0.001)	16.7–27.4	0.400 (0.327)
	Moderate	9	59.84	19.92 (0.011)	26.8–35.0	0.00 (1.00)
	Severe	12	70.19	36.90 (<0.001)	30.6–35.9	0.182 (0.411)
Miscarriage/spontaneous abortion	Moderate	7	63.90	16.62 (0.011)	14.1–18.9	−0.524 (0.099)
	Severe	10	70.24	30.24 (<0.001)	33.0–39.0	−0.511 (0.040)
Preterm delivery	Mild	4	0.00	2.64 (0.450)	5.1–6.3	−0.667 (0.174)
	Moderate	9	0.00	6.81 (0.557)	13.0–14.2	−0.44 (0.095)
	Severe	17	76.72	68.74 (<0.001)	47.6–53.1	0.015 (0.934)
Small for gestational age	Mild	4	55.74	6.78 (0.079)	13.2–15.9	−0.667 (0.308)
	Moderate	9	61.42	20.74 (0.008)	12.4–14.5	−0.056 (0.917)
	Severe	14	69.50	42.62 (<0.001)	33.2–39.2	0.00 (1.00)
Therapeutic abortion	Severe	6	86.25	36.36 (<0.001)	5.5–14.1	−0.60 (0.142)

Table 5. Summary of Heterogeneity, Sensitivity Analysis, and Publication Bias for Pooled Maternal Outcomes

Outcome	Group	Number of Studies	I^2	Cochran's Q (*P* Value)	Sensitivity Analysis (Min–Max)	Begg and Madzumdar Rank Correlation—Tau (*P* Value)
Arrhythmia	Mild	7	0	5.16 (0.523)	2.9–3.6	−0.143 (0.652)
	Moderate	12	61.56	28.61 (0.003)	6.7–9.5	0.212 (0.337)
	Severe	17	58.44	38.50 (0.001)	11.2–14.1	0.044 (0.805)
Heart failure	Moderate	12	32.78	16.36 (0.128)	2.1–3.6	0.394 (0.075)
	Severe	17	69.26	45.54 (<0.001)	11.8–17.4	0.371 (0.054)
Hypertensive diseases of pregnancy	Mild	4	0.00	0.220 (0.974)	11.1–11.6	0.333 (0.500)
	Moderate	7	19.79	7.48 (0.279)	10.7–13.0	−0.149 (0.652)
	Severe	12	56.13	25.07 (0.009)	8.6–14.6	−0.242 (0.276)
Postpartum hemorrhage	Mild	6	0.00	0.59 (0.989)	10.3–10.5	−0.467 (0.188)
	Moderate	8	0.00	6.43 (0.491)	10.0–11.1	−0.357 (0.216)

are notable maternal morbidities as well as neonatal mortality and morbidity, particularly as severity of CHD in the mother increases.

The risk of neonatal death was 3.5 times higher in neonates born to women with severe CHD lesions when compared with those born to women with milder forms of CHD (Table 3). The rates of neonatal death among all severity groups exceeds the previously estimated overall rate of 1.7% among all women with CHD.[4] The risk of neonatal death in this study was primarily driven by relatively high rates among offspring of women with Eisenmenger's syndrome and Ebstein's anomaly. Abnormal uteroplacental blood flow is the suspected mechanism behind pregnancy and neonatal complications. As such, it is unsurprising that lesions causing cyanotic heart disease might have the most profound impact on pregnancy outcomes.[44–47] Overall, the number of parturients with CHD are growing faster than the number of women delivering without heart disease. Although the awareness of risks of CHD pregnancy and the number of multidisciplinary programs caring for these women have increased, our findings reveal that there are still important gaps in outcomes and underscore the need for further prenatal and obstetric research.[48]

The risks of C-section, preterm delivery, and being born SGA are all markedly increased as severity of maternal CHD increases. There are a number of reasons for increased rates of C-section among women with more severe CHD. These include decisions against vaginal delivery premised on changes in hemodynamics caused by the pushing (Valsalva), concern for hemorrhage in anticoagulated patients, exacerbation of pulmonary hypertension in patients with cyanotic disease, and logistical ease.[32] Rates of maternal deterioration and unplanned delivery as well as iatrogenic preterm labor are higher among women with CHD as well.[4] Our study found rates of C-section delivery to be highest among parturients with Eisenmenger's and Fontan, likely because of maternal decompensation in the third trimester often followed by emergency C-section among these populations.[47] Rates of C-section were also elevated among women with history of ToF, which may be attributable to greater caution among obstetricians caring for more vulnerable mothers and offspring.[49] Unplanned delivery owing to maternal deterioration may underpin the increased rates of preterm birth and SGA delivery among CHD pregnancies.[48] As discussed previously, rates of preterm birth and SGA delivery in our study were most pronounced among women with Fontan and Eisenmenger's syndrome, which is to be expected given the severity of their respective lesions. This study also revealed increased rates of recurrence of some form of CHD in neonates born to mothers with more severe CHD. This trend has been previously established, as in the cases of left-sided outflow tract obstructions and autosomal dominant lesions such as conotruncal abnormalities and ToF caused by 22q.11 mutations. These types of CHD typically fall in the more severe World Health Organization categories (III and IV), thus clarifying the foundation of the relationship found between severity group and recurrence rate. Previous estimates range between 0% and 50% transmission, averaging 3% to 4% transmission among mothers with de novo mutations. The present meta-analysis establishes a more precise estimate of risk among specific risk-stratified CHD groups.[47]

The severity of CHD and likelihood of miscarriage/spontaneous abortion also correlate, but this relationship is likely diminished by the exclusion of nonviable pregnancies in some studies. Too few studies reported on the rate of therapeutic abortion among women with CHD to aggregate and assess for trends, but studies suggest that increased counseling on contraception and recommendations of abstinence by medical professionals may decrease the rate of pregnancy in this population.[32]

In contrast to the risk of neonatal mortality, the risks of maternal morbidity and mortality are less pronounced. Maternal mortality is less commonly reported than neonatal mortality and thus less clearly correlated with severity of CHD. This figure is affected by the studies that excluded deceased women from retrospective review and survey. This low rate of maternal death is concordant with previous large-population studies, underpowered for the purposes of drawing conclusions about trends among pregnant women with CHD.[4,48] For instance, a study of over 3 million women including over 3000 hospitalized parturients with CHD was unable to show a difference in mortality rates between the study groups.[50]

Although the end point of maternal mortality did not correlate to the severity of CHD, the risk of morbidities including arrhythmia and heart failure clearly increase as CHD severity increases. Regarding specific lesions, prior systematic review suggests similar rates of arrhythmia among women with Fontan, TGA, and ToF, whereas estimated rates of arrhythmia among those with Eisenmenger's syndrome and Ebstein's anomaly were significantly lower (0% and 3.9%, respectively) than our own (39.4% and 20.9%, respectively) (Table S2).[4] In the case of Eisenmenger's, this may be because of small sample size, as well as the presence of significant heterogeneity among our population, including data published by Katsurahgi et al.[28] Regarding the trends seen among women with Ebstein's anomaly, parturients commonly have a history of Wolff-Parkinson-White syndrome or other supraventricular arrhythmia and are known to develop atrial flutter in pregnancy, thus substantiating this study's relatively high estimate of their risk for arrhythmia in pregnancy.[27]

Heart failure risk increases with lesion severity and this may be an underestimate given heart failure is a common reason for elective abortion, especially among women with severe CHD.[50] This trend is driven by high rates of heart failure among parturients with Eisenmenger's syndrome, in some studies as high as 100%.[51] Heart failure can be difficult to assess in pregnancy as some of the symptoms including dyspnea, fatigue, and swelling share features with normal pregnancy.[16] Women were included if they were diagnosed with heart failure or met 3 of the diagnostic criteria, which may have led to inconsistencies in the validity of diagnosis within this analysis.

Several limitations exist within this study. First, because of the variation in study populations, there is heterogeneity in the data analyzed. As discussed, populations varied in their inclusion of deceased women and nonviable pregnancies. Some heterogeneity also exists among diagnostic criteria for reported outcomes such heart failure, which are coded differently by various medical systems internationally. Likewise, there was variation in correction and cardiac function amongst women included in CHD groups, not captured in this study because of heterogenous reporting. Additionally, observational studies relying on surveys introduce recall bias, which cannot be solved at a meta-analysis level. However, no evidence of publication bias was found.

CONCLUSIONS

Overall, this study finds that the rates of morbidity and mortality among offspring of women with CHD is greater for those born to women with more severe diagnoses. This includes risk of surgical delivery, miscarriage or spontaneous abortion, preterm delivery, recurrence of CHD in the neonate, and SGA delivery. Further, there is a clear correlation with specific maternal morbidities and CHD severity, such as heart failure and arrhythmia.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S6
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Medline Search Strategy.

▼ **Search History** (11)

# ▲	Searches	Results	Type
1	exp Pregnancy Outcome/ or exp Pregnancy Complications/ or exp Pregnancy/ or exp Obstetrics/ or exp Labor, Obstetric/ or exp Delivery, obstetric/ or exp parturition/ or exp Pregnant Women/ or exp Pregnancy, High-Risk/ or pregnancy complication*.ti,ab. or pregnancy outcome*.ti,ab. or high risk pregnanc*.ti,ab. or (pregnant and (woman or women)).ti,ab. or (pregnancy or pregnant or obstetric*).ti,ab. or ((vaginal or cesarean or caesarean) and (birth or delivery)).ti,ab. or childbirth.ti,ab. or prenatal.ti,ab. or postnatal.ti,ab. or (obstetric adj2 delivery).ti,ab. or (obstetric adj2 labor).ti,ab. or (pregnancy adj2 disorder*).ti,ab. or parturition.ti,ab.	1055379	Advanced
2	exp Heart Defects, Congenital/ or exp Heart Septal Defects/ or exp Heart Septal Defects, atrial/ or exp Heart Septal Defects, ventricular/ or exp Aortic Valve Stenosis/ or exp aortic stenosis/ or exp Pulmonary Valve Stenosis/ or exp pulmonary atresia/ or exp Tetralogy of Fallot/ or exp Aortic Coarctation/ or exp Hypoplastic Left Heart Syndrome/ or exp Fontan Procedure/ or exp Norwood Procedure/ or exp Transposition of Great Vessels/ or exp Ebstein Anomaly/ or exp Eisenmenger Complex/ or exp Hypertension, Pulmonary/ or (congenital adj1 heart).ti,ab. or cardiac malformation*.ti,ab. or (abnormalit* adj1 heart).ti,ab. or (malformation adj1 heart).ti,ab. or (block adj1 heart).ti,ab. or (defect* adj1 heart).ti,ab. or septal defect*.ti,ab. or (septal adj2 defect*).ti,ab. or (aortic adj2 stenosis).ti,ab. or (valve adj2 stenosis).ti,ab. or pulmonary valve stenosis.ti,ab. or pulmonary atresia.ti,ab. or (pulmon* adj2 atresia*).ti,ab. or fallot.ti,ab. or (Aort* adj3 Coarctation).ti,ab. or (left heart adj2 hypopla*).ti,ab. or fontan.ti,ab. or norwood procedure.ti,ab. or (Glenn and (Procedure or shunt)).ti,ab. or (transposition* adj3 arteries).ti,ab. or (transposition* adj3 vessels).ti,ab. or (ebstein* adj2 anomol*).ti,ab. or (ebstein* adj2 malformation*).ti,ab. or (Eisenmenger* adj2 complex).ti,ab. or (Eisenmenger* adj2 syndrome).ti,ab. or (pulmon* adj1 hypertension).ti,ab. or cyanotic heart.ti,ab.	243672	Advanced
3	exp maternal death/ or exp perinatal mortality/ or exp perinatal death/ or exp maternal mortality/ or exp Pregnancy Complications, Cardiovascular/ or exp Obstetric Labor, Premature/ or exp Hypertension, Pregnancy-Induced/ or exp Pre-Eclampsia/ or exp eclampsia/ or exp HELLP syndrome/ or exp thromboembolism/ or exp stroke/ or exp heart failure/ or exp Postpartum Hemorrhage/ or exp heart arrest/ or exp Myocardial Infarction/ or exp endocarditis/ or exp Abortion, Spontaneous/ or exp Abortion, Therapeutic/ or exp Arrhythmias, Cardiac/ or (maternal adj1 death*).ti,ab. or (pregnancy adj2 death*).ti,ab. or (mother adj2 death*).ti,ab. or (maternal adj2 morbidit*).ti,ab. or maternal mortality.ti,ab. or perinatal mortality.ti,ab. or perinatal death.ti,ab. or (cardiovascular adj2 pregnancy complication*).ti,ab. or (maternal adj2 complication*).ti,ab. or (maternal adj2 outcome*).ti,ab. or ((preterm or premature) and delivery).ti,ab. or (premature adj2 labor).ti,ab. or premature labor.ti,ab. or (pregnancy adj2 hypertension).ti,ab. or maternal hypertension.ti,ab. or pre-eclampsia.ti,ab. or	1057301	Advanced

		preeclampsia.ti,ab. or eclampsia.ti,ab. or HELLP Syndrome.ti,ab. or hemolysis elevated liver enzymes low platelets.ti,ab. or Thromboembolism.ti,ab. or embolism.ti,ab. or embolus.ti,ab. or cerebrovascular accidents.ti,ab. or stroke.ti,ab. or ((cardiac or heart) and failure).ti,ab. or postpartum hemorrhage.ti,ab. or (cardiac adj2 arrest).ti,ab. or (heart adj2 arrest).ti,ab. or ((Myocardial or cardiac or heart) and Infarction*).ti,ab. or endocarditis.ti,ab. or spontaneous abortion.ti,ab. or miscarriage.ti,ab. or therapeutic abortion.ti,ab. or medical abortion.ti,ab. or (cardiac adj2 arrhythmia*).ti,ab. or (heart adj2 arrhythmia*).ti,ab.		
☐	4	exp infant mortality/ or exp stillbirth/ or exp fetal mortality/ or exp fetal death/ or exp premature birth/ or exp infant death/ or exp Infant, Small for Gestational Age/ or exp Fetal Growth Retardation/ or infant mortality.ti,ab. or infant morbidity.ti,ab. or (stillbirth or stillborn).ti,ab. or infant death.ti,ab. or fetal mortality.ti,ab. or (fetal adj2 death).ti,ab. or endocarditis.ti,ab. or intrauterine growth retardation.ti,ab. or (Small adj2 Gestational adj2 Age).ti,ab. or Fetal Growth Retardation.ti,ab. or (neonatal adj2 outcome*).ti,ab. or premature birth.ti,ab.	142863	Advanced
☐	5	1 and 2 and 3 and 4	1084	Advanced
☐	6	limit 5 to (english language and yr="2007 -Current")	492	Advanced
☐	7	6 not CASE REPORT$.ti,ab,pt.	410	Advanced
☐	8	7 not peripartum cardiomyopath*.ti.	410	Advanced
☐	9	8 not hypertrophic cardiomyopath*.ti.	407	Advanced
☐	10	9 not ((exp animal/ or nonhuman/) not exp human/)	391	Advanced
☐	11	10 not (rat* or mice or mouse or pig*).ti.	384	Advanced

Embase Search Strategy

▼ **Search History** (11)

# ▲	Searches	Results	Type
1	exp infant mortality/ or exp stillbirth/ or exp fetus mortality/ or exp fetus death/ or exp small for date infant/ or exp intrauterine growth retardation/ or exp high risk infant/ or infant mortality.ti,ab. or infant morbidity.ti,ab. or (stillbirth or stillborn).ti,ab. or infant death.ti,ab. or fetal mortality.ti,ab. or (fetal adj2 death).ti,ab. or intrauterine growth retardation.ti,ab. or intrauterine growth restriction.ti,ab. or (Small adj2 Gestational adj2 Age).ti,ab. or Fetal Growth Retardation.ti,ab. or Fetal Growth restriction.ti,ab. or (neonatal adj2 outcome*).ti,ab. or premature birth.ti,ab.	106775	Advanced
2	exp pregnancy outcome/ or exp pregnancy/ or exp pregnant woman/ or exp childbirth/ or exp high risk pregnancy/ or exp Obstetrics/ or exp obstetric patient/ or exp labor/ or exp Delivery/ or exp prenatal care/ or (pregnancy adj2 outcome$).ti,ab. or pregnan$.ti,ab. or (pregnant adj1 wom?n).ti,ab. or childbirth.ti,ab. or parturition.ti,ab. or (pregnancy adj2 high risk).ti,ab. or obstetric$.ti,ab. or labor.ti,ab. or (obstetric adj2 delivery).ti,ab. or ((vaginal or cesarean or caesarean) and (birth or delivery)).ti,ab. or prenatal.ti,ab. or postnatal.ti,ab.	850635	Advanced
3	exp congenital heart malformation/ or exp congenital heart disease/ or exp heart septum defect/ or exp heart atrium septum defect/ or exp heart ventricle septum defect/ or exp aortic stenosis/ or exp aortic valve stenosis/ or exp pulmonary valve atresia/ or exp pulmonary valve stenosis/ or exp Fallot tetralogy/ or exp aortic coarctation/ or exp hypoplastic left heart syndrome/ or exp Fontan procedure/ or exp Norwood procedure/ or exp Glenn shunt/ or exp great vessels transposition/ or exp Ebstein anomaly/ or exp Eisenmenger complex/ or exp pulmonary hypertension/ or exp cyanotic heart disease/ or (congenital heart adj2 defects).ti,ab. or (heart adj2 malform$).ti,ab. or ((congenital or abnormalit$ or malformation or block or defect$) adj2 heart).ti,ab. or (cardiac adj2 malformation$).ti,ab. or (congenital heart adj2 diseases).ti,ab. or (septal and (malformation$ or defect$)).ti,ab. or (atrial septal adj2 defect$).ti,ab. or (ventric$ adj1 sept$ adj2 defect).ti,ab. or ((aortic or valve) adj2 stenosis).ti,ab. or (pulmon$ adj2 atresia$).ti,ab. or (pulmonary valve adj2 stenosis).ti,ab. or fallot.ti,ab. or (aort$ adj2 coarctation$).ti,ab. or Hypoplastic Left Heart Syndrome.ti,ab. or fontan.ti,ab. or norwood procedure.ti,ab. or (glenn adj2 procedure).ti,ab. or (Transposition adj2 Great Vessels).ti,ab. or (transposition$ adj2 arteries).ti,ab. or (transposition$ adj3 vessels).ti,ab. or (ebstein adj2 (anomol$ or malformation$)).ti,ab. or (Eisenmenger adj2 (complex or syndrome)).ti,ab. or (pulmon$ adj1 hypertension).ti,ab. or (cyanotic adj1 heart).ti,ab.	241335	Advanced
4	exp maternal death/ or exp maternal mortality/ or exp maternal morbidity/ or exp pregnancy complication/ or exp preterm delivery/ or exp hypertension/ or exp maternal hypertension/ or exp eclampsia/ or exp HELLP syndrome/ or exp preeclampsia/ or exp thromboembolism/ or exp cerebrovascular accident/ or exp heart failure/ or exp Postpartum Hemorrhage/ or exp obstetric hemorrhage/ or exp heart arrest/ or exp heart	2105695	Advanced

		infarction/ or exp endocarditis/ or exp spontaneous abortion/ or exp induced abortion/ or exp heart arrhythmia/ or (maternal adj1 death*).ti,ab. or (pregnancy adj2 death*).ti,ab. or (mother adj2 death*).ti,ab. or maternal mortality.ti,ab. or perinatal mortality.ti,ab. or perinatal death.ti,ab. or (maternal adj2 morbidit$).ti,ab. or (cardiovascular adj2 pregnancy complication*).ti,ab. or (maternal adj2 complication*).ti,ab. or (maternal adj2 outcome*).ti,ab. or ((preterm or premature) and delivery).ti,ab. or (premature adj2 labor).ti,ab. or premature labor.ti,ab. or (pregnancy adj2 hypertension).ti,ab. or maternal hypertension.ti,ab. or pre-eclampsia.ti,ab. or preeclampsia.ti,ab. or eclampsia.ti,ab. or HELLP Syndrome.ti,ab. or hemolysis elevated liver enzymes low platelets.ti,ab. or Thromboembolism.ti,ab. or embolism.ti,ab. or embolus.ti,ab. or cerebrovascular accidents.ti,ab. or stroke.ti,ab. or heart failure.ti,ab. or postpartum hemorrhage.ti,ab. or (cardiac adj2 arrest).ti,ab. or Myocardial Infarction.ti,ab. or endocarditis.ti,ab. or spontaneous abortion.ti,ab. or miscarriage.ti,ab. or therepeutic abortion.ti,ab. or medical abortion.ti,ab. or (cardiac adj2 arrhythmia*).ti,ab. or (heart adj2 arrhythmia*).ti,ab.		
☐	5	1 and 2 and 3 and 4	2481	Advanced
☐	6	limit 5 to (english language and yr="2007 -Current")	1948	Advanced
☐	7	6 not CASE REPORT$.ti,ab,pt.	1812	Advanced
☐	8	7 not peripartum cardiomyopath*.ti.	1810	Advanced
☐	9	8 not hypertrophic cardiomyopath*.ti.	1808	Advanced
☐	10	9 not ((exp animal/ or nonhuman/) not exp human/)	1793	Advanced
☐	11	10 not (rat* or mice or mouse or pig*).ti.	1773	Advanced

Cochrane Search Strategy

▼ **Search History** (5)

# ▲	Searches	Results
2	((maternal adj1 death*) or (pregnancy adj2 death*) or (mother adj2 death*) or (maternal adj2 morbidit*) or maternal mortality or perinatal mortality or perinatal death or (cardiovascular adj2 pregnancy complication*) or (maternal adj2 complication*) or (maternal adj2 outcome*) or ((preterm or premature) and delivery) or (premature adj2 labor) or premature labor or (pregnancy adj2 hypertension) or maternal hypertension or pre-eclampsia or preeclampsia or eclampsia or HELLP Syndrome or hemolysis elevated liver enzymes low platelets or Thromboembolism or embolism or embolus or cerebrovascular accidents or stroke or ((cardiac or heart) and failure) or postpartum hemorrhage or (cardiac adj2 arrest) or (heart adj2 arrest) or ((Myocardial or cardiac or heart) and Infarction*) or endocarditis or spontaneous abortion or miscarriage or therapeutic abortion or medical abortion or (cardiac adj2 arrhythmia*) or (heart adj2 arrhythmia*)).ti,ab.	1001
3	(infant mortality or infant morbidity or (stillbirth or stillborn) or infant death or fetal mortality or (fetal adj2 death) or endocarditis or intrauterine growth retardation or (Small adj2 Gestational adj2 Age) or Fetal Growth Retardation or (neonatal adj2 outcome*) or premature birth).ti,ab.	180
4	((congenital adj1 heart) or cardiac malformation* or (abnormalit* adj1 heart) or (malformation adj1 heart) or (block adj1 heart) or (defect* adj1 heart) or septal defect* or (septal adj2 defect*) or (aortic adj2 stenosis) or (valve adj2 stenosis) or pulmonary valve stenosis or pulmonary atresia or (pulmon* adj2 atresia*) or fallot or (Aort* adj3 Coarctation) or (left heart adj2 hypopla*) or fontan or norwood procedure or (Glenn and (Procedure or shunt)) or (transposition* adj3 arteries) or (transposition* adj3 vessels) or (ebstein* adj2 anomol*) or (ebstein* adj2 malformation*) or (Eisenmenger* adj2 complex) or (Eisenmenger* adj2 syndrome) or (pulmon* adj1 hypertension) or cyanotic heart).ti,ab.	43
5	1 and 2 and 3 and 4	1

Table S2. Count of Maternal Outcomes by Lesion (highlights indicate enough studies to pool estimates).

Outcome	AS	ASD	ccTGA	CoA	DORV	Ebstein's	Eisenmenger's	Fontan	PA	PDA	PS	TGA	ToF	VSD
Arrhythmia	1	3	2	2	1	4	4	5	2	1	2	6	4	3
Cardiac Arrest	3	2	2	3	1	2	1	3	1	1		3	4	3
Endocarditis	2	3	1	1	1	2	2	2	2		1	3	3	3
Heart Failure	1	3	2	2		4	5	4	2	1	2	5	4	3
Hypertensive diseases of pregnancy	1	2	2	2	1	1	3	5	1		1	2	3	2
Maternal Mortality	5	6	3	5	2	7	6	6	3	3	4	8	10	6
Post-partum hemorrhage	2	3	1	2	1	2	3	3	1		1	2	4	3
Thromboembolic Event	1	2	2	2	2		4	4	2	1	1	4	4	2
Grand Total	**16**	**24**	**15**	**19**	**9**	**22**	**28**	**35**	**14**	**7**	**12**	**33**	**36**	**25**

Table S3. Count of Neonatal Outcomes by Lesion (highlights indicate enough studies to pool estimates).

Outcomes	AS	ASD	ccTGA	CoA	DORV	Ebstein's	Eisenmenger's	Fontan	PA	PDA	PS	TGA	ToF	VSD
C-section	1	2	1	2	2	2	4	5		1	1	3	4	2
Miscarriage/Spontaneous Abortion		1	1	1	1		2	4	1		2	2	4	1
Neonatal Mortality	4	5	3	4	2	5	7	7	4	2	3	7	8	6
Premature/preterm delivery	1	2	2	2	1	2	4	5	1		1	6	4	2
Recurrence	1	2	1	1	1	1	2	6	1		2	5	6	2
SGA	1	2	2	2	1	2	4	4	1		1	4	4	2
Therapeutic Abortion		1	1	1	1		1	3				1	2	1
Grand Total	**8**	**15**	**11**	**13**	**9**	**12**	**24**	**34**	**8**	**3**	**10**	**28**	**32**	**16**

Table S4. Individual Lesion Estimates for Select Maternal Outcomes with N ≥ 4 Studies.

Outcome	Lesion	Number of Events	Total Sample Size	% (95% CI)
Maternal Mortality	AS	0	78	0.00 (0.00 – 4.62)*
	ASD	1	115	0.87 (0.02 – 4.75)*
	CoA	0	71	0.00 (0.00 – 5.06)*
	Ebstein's	0	46	0.00 (0.00 – 7.71)*
	Eisenmenger's	6	46	13.04 (4.94 – 26.26)
	Fontan	0	236	0.00 (0.00 – 1.55)*
	PS	0	80	0.00 (0.00 – 4.51)*
	TGA	2	183	1.09 (0.13 – 3.89)*
	ToF	0	343	0.00 (0.00 – 1.07)*
	VSD	0	120	0.00 (0.00 – 3.03) *
Arrhythmia	Ebstein's	10	54	20.9 (10.4 – 37.6)
	Eisenmenger's	13	33	39.4 (22.9 – 57.9)*
	Fontan	19	244	10.3 (3.8 – 25.3)
	TGA	24	217	11.8 (6.7 – 20.1)
	ToF	11	246	6.0 (3.3 – 10.5)
Heart Failure	Ebstein's	3	54	5.6 (1.2 – 15.4)*
	Eisenmenger's	25	34	69.5 (26.7 – 93.4)
	Fontan	14	231	6.1 (3.6 – 10.0)
	TGA	7	159	6.1 (2.9 – 12.2)
	ToF	3	246	2.8 (0.5 – 15.3)
Hypertensive Diseases of Pregnancy	Fontan	6	244	3.6 (1.2 – 10.4)
Post-Partum Hemorrhage	Fontan	26	233	11.2 (7.4 – 15.9)*
	ToF	17	215	8.7 (5.5 – 13.6)
Thrombolytic Event	Eisenmenger's	2	56	3.6 (0.4 – 12.3)*
	TGA	1	98	1.0 (0.03 – 5.6)*
	ToF	1	214	0.5 (0.01 – 2.6)*

* Too events to pool estimates. Results are presented as raw percentage with an exact 95% confidence interval

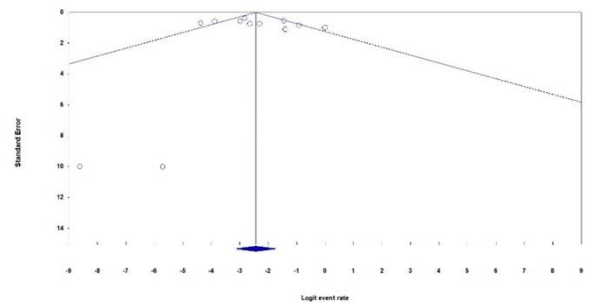
Table S5. Individual Lesion Estimates for Select Neonatal Outcomes with N ≥ 4 Studies.

Outcome	Lesion	Number of Events	Total Sample Size	% (95% CI)
Neonatal Mortality	AS	1	129	0.8 (0.02 – 4.2)*
	ASD	6	439	1.4 (0.50, 2.95)*
	CoA	6	202	3.0 (1.1 – 6.4)*
	Ebstein's	2	35	5.7 (0.7 – 19.2)*
	Eisenmenger's	3	53	5.7 (1.2 – 15.7)*
	Fontan	6	162	3.7 (1.4 – 7.9)*
	PA	0	19	0.0 (0.0 – 17.7)*
	TGA	5	143	3.5 (1.2 – 8.0)*
	ToF	7	297	2.4 (0.1 – 4.8)*
	VSD	2	332	0.6 (0.07 – 2.2)*
C-Section	Eisenmenger's	26	26	94.4 (76.4 – 98.9)
	Fontan	65	120	53.7 (44.6 – 62.5)
	ToF	35	148	25.5 (18.7 – 33.8)
Miscarriage/ Spontaneous Abortion	Fontan	131	272	46.2 (34.8 – 58.1)
	ToF	61	331	16.5 (9.8 - 26.4)
Preterm Delivery	Eisenmenger's	20	29	67.7 (18.0 – 95.2)
	Fontan	101	139	72.0 (63.8 – 79.0)
	TGA	47	158	32.7 (25.4 – 40.8)
	ToF	35	249	14.7 (10.8 – 19.9)
Recurrence	Fontan	5	141	3.5 (1.16 – 8.08)*
	TGA	1	107	0.9 (0.02 – 5.10)*
	ToF	13	290	5.0 (2.9 – 8.4)
SGA	Eisenmenger's	17	29	62.3 (34.6 – 83.8)
	Fontan	45	117	37.7 (15.8 – 66.1)
	TGA	31	110	29.6 (14.7 – 50.6)
	ToF	43	249	18.9 (10.4 – 32.0)

Table S6. MINORS rating scale.

		Methodological items for non-randomized studies								*Additional criteria in the case of comparative study*					
Study	**Study Type**	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	**Total**	**Out of**
Balci (2014[9]	Prospective Cohort	2	2	2	2	2	2	2	2	NA	NA	NA	NA	16	16
Bonner (2017)[10]	Case Series	2	2	2	2	0	2	2	2	NA	NA	NA	NA	14	16
Brun (2018)[11]	Retrospective Cohort	2	2	2	2	0	2	0	2	2	2	2	2	20	24
Cataldo (2016)[12]	Retrospective Cohort	2	2	2	2	0	2	2	0	2	2	2	0	18	24
Cauldwell (2018)[13]	Retrospective Cohort	2	2	2	2	0	2	0	0	NA	NA	NA	NA	10	16
Chopra (2010)[14]	Case Series	2	2	2	2	0	2	0	0	NA	NA	NA	NA	10	16
Drenthen (2008)[15]	Retrospective Cohort	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12	16
Drenthen (2010)[16]	Retrospective Cohort	2	2	2	1	0	2	2	2	NA	NA	NA	NA	13	16
Duan (2016)[17]	Case Series	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12	16
Egbe (2019)[18]	Retrospective Cohort	2	2	2	2	0	2	2	2	2	2	2	2	22	24
Ford (2008)[19]	Retrospective Cohort	2	2	2	2	0	0	2	0	NA	NA	NA	NA	10	16
Gelson (2008)[20]	Retrospective Cohort	2	2	2	2	0	2	2	2	2	2	2	2	22	24
Gelson (2011)[21]	Retrospective Cohort	2	2	2	1	0	2	2	0	2	2	2	2	18	24
Gouton (2015)[22]	Retrospective Cohort	2	2	2	2	0	2	2	2	NA	NA	NA	NA	14	16
Hidano (2011)[23]	Retrospective Cohort	2	2	2	1	0	2	2	0	NA	NA	NA	NA	11	16
Jain (2011)[24]	Retrospective Cohort	2	2	2	2	0	2	2	2	2	2	2	2	22	24

Jimenez-Juan (2014)[25]	Retrospective Cohort	2	2	2	2	0	2	2	2	NA	NA	NA	NA	14	16
Kampman (2017)[26]	Prospective Cohort	2	2	2	2	2	2	2	2	2	2	2	2	24	24
Katsuragi (2013)[27]	Case Series	2	2	2	1	0	2	2	0	NA	NA	NA	NA	11	16
Katsurahgi (2019)[28]	Case Series	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12	16
Kowalik (2014)[29]	Retrospective Cohort	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12	16
Ladouceur (2017)[30]	Case Series	2	2	2	2	2	2	2	2	NA	NA	NA	NA	16	16
Metz (2011)[31]	Retrospective Cohort	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12	16
Michaelson-Cohen (2011)[32]	Prospective Cohort	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12	16
Pedersen (2008)[33]	Retrospective Cohort	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12	16
Phillips (2019)[34]	Case Series	2	0	2	2	0	2	2	0	NA	NA	NA	NA	10	16
Pillutla (2016)[35]	Retrospective Cohort	2	2	2	1	0	2	2	2	NA	NA	NA	NA	13	16
Pundi (2016)[36]	Retrospective Cohort	2	2	2	2	0	2	2	0	2	2	2	0	18	24
Song (2008)[37]	Retrospective Cohort	2	2	2	1	0	2	2	2	2	2	2	2	21	24
Tobler (2010)[38]	Retrospective Cohort	2	2	2	2	0	2	0	0	NA	NA	NA	NA	10	16
Wang (2011)[39]	Case Series	2	2	2	1	0	2	2	0	NA	NA	NA	NA	11	16
Yap (2009)[40]	Retrospective Cohort	2	2	2	2	0	2	2	2	NA	NA	NA	NA	14	16
Yap (2010)[41]	Retrospective Cohort	2	2	2	2	0	2	2	2	NA	NA	NA	NA	14	16
Zentner (2012)[42]	Retrospective Cohort	2	2	2	2	0	2	0	0	2	2	2	0	16	24



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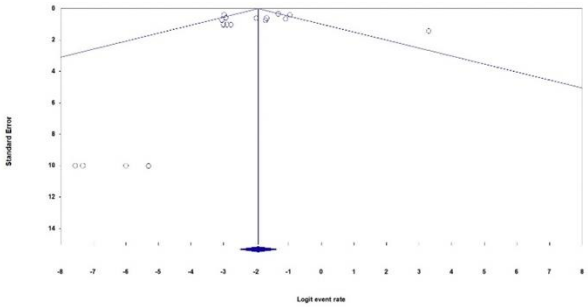

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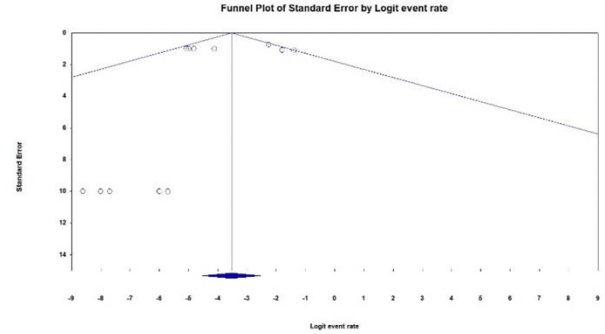

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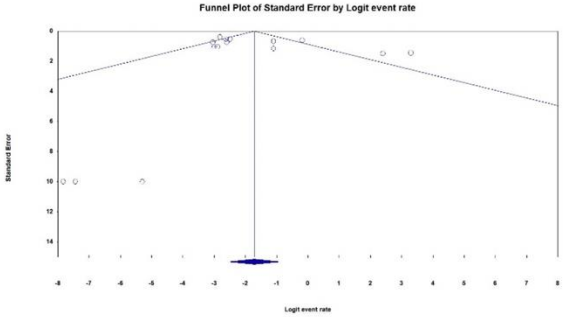

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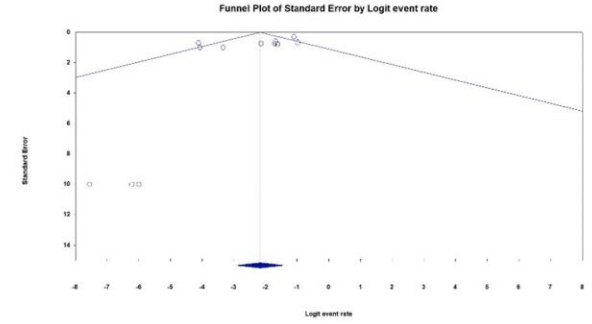
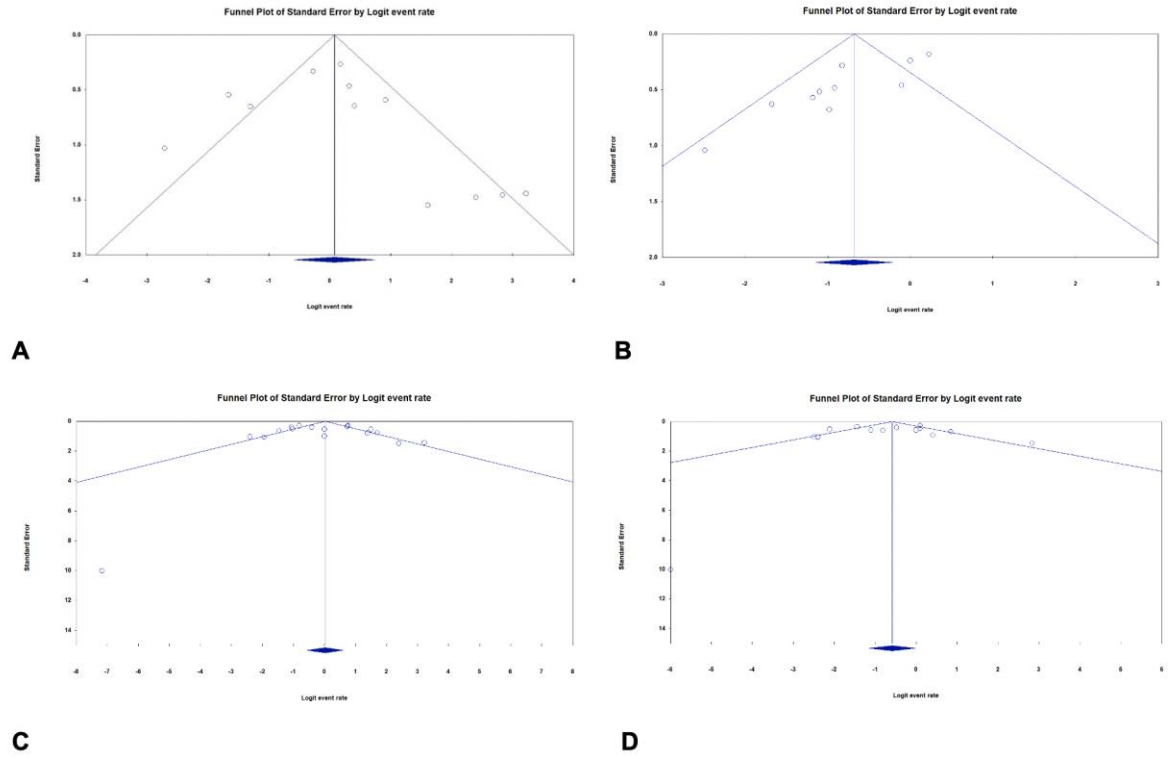


E

Supplemental Figure 1a-e. Funnel plots for lesions severity groups with more than 10 studies. A) Arrhythmia- Moderate CHD; B) Arrhythmia- Severe CHD; C) Heart Failure- Moderate CHD; D) Heart Failure- Severe CHD; E) Hypertensive disease – Severe



Supplemental Figure 2a-d. Funnel plots for lesions severity groups with more than 10 studies. A) C-Section - Severe CHD; B) Miscarriage/Spontaneous abortion- Severe CHD; C) Preterm Delivery- Severe CHD; D) SGA-Severe; Events clustered at standard error = 10 are studies with 0 events where the event rate of 0.001 has been imputed.